02-08-06

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Issued Patent No.	:	6,828,450
Issue Date	:	December 7, 2004
Appl. No.	:	09/974,716
Filing Date:	:	October 9, 2001
TC/A.U.	:	1621
Examiner	:	Sikarl A. Witherspoon
Applicant	:	Hua et al.
For	:	Triptycene Analogs
Docket No.	:	74-00
Customer No.	:	23713

Certificate
FEB 10 2006
of Correction

Commissioner for Patents
Attention: Certificate of Correction Branch
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING
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PO Box 1450, Alexandria, VA 22313-1450

February 7, 2006
Date

Cathy Nelson
Cathy Nelson

EV 758 237 883 US
Express Mail Tracking Number

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. 1.322

Sir:

Please issue a Certificate of Correction for U. S. Patent 6,828,450, as errors appear in the printed patent. Enclosed are two copies of Form PTO/SB/44 with the errors listed thereon. Also enclosed are copies of the specification pages referred to herein.

The addition of the Hua reference on the front page was listed on the Supplemental Information Disclosure Statement filed June 8, 2004 and initialed by the Examiner.

The printing errors appeared correctly in the application, as shown by the enclosed copies of the specification pages as originally filed. Specifically, the error in column 5, line 52, appears correctly on page 9 of the application as originally filed.

The error in column 6, lines 28-50, appears correctly on page 9 of the application as originally filed.

The error in column 7, lines 13-27, appears correctly on page 10 of the application as originally filed.

The error in column 15, line 52, appears correctly on page 23, line 2 of the application as originally filed.

The error in column 34, lines 57-65, appears correctly on page 49, lines 1-10 of the application as originally filed.

The error in column 37, lines 23-63, Scheme 6, appears correctly on page 50 of the application as originally filed.

The error in column 40, line 24, appears correctly on page 52 of the application as originally filed.

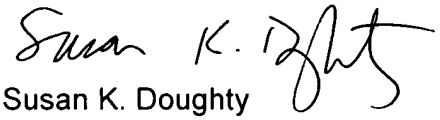
The error in column 41, line 32, Scheme 10, appears correctly on page 53 of the application as originally filed.

The error in column 53, line 11, appears correctly on page 65, line 25 of the application as originally filed.

The error in column 66, lines 38-64, Scheme 17, appears correctly on page 83 of the application as originally filed.

It is believed that the present submission does not require the payment of any fees. If this is incorrect however, please charge any required fee to Deposit Account No. 07-1969.

Respectfully submitted,



Susan K. Doughty
Reg. No. 43,595

GREENLEE, WINNER AND SULLIVAN, P.C.
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E-mail: winner@greenwin.com
Attorney Docket No. 74-00
February 7, 2006

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CERTIFICATE OF CORRECTION

PATENT NO. : **6,828,450 B2**

APPLICATION NO. : **09/974,716**

ISSUE DATE : **December 7, 2004**

INVENTOR(S) : **Hua et al.**

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Front Page:

Under heading "References Cited" under "U.S. PATENT DOCUMENTS", please add the following
--5,958,970 9/1999 Hua et al.....514/555--.

In the Specification:

Column 5, line 52, replace "TT2:X = PMe, Y = H" with -- TT2:X = OMe, Y = H --.

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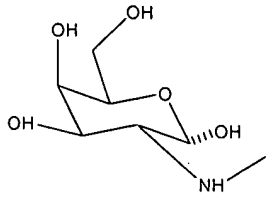
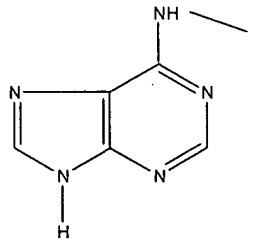
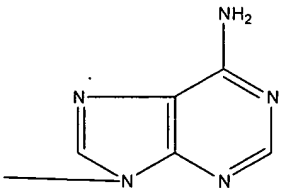
Column 6, lines 28-50, move the structures --



N analog 3: Y = Br, X =



N analog 4: X = OMe, Y = Br, R^2 =



S analog 9: Y = Br, X = $SCH_2CH(CO_2H)NH_2$ -- to the bottom of column 5 after X =.

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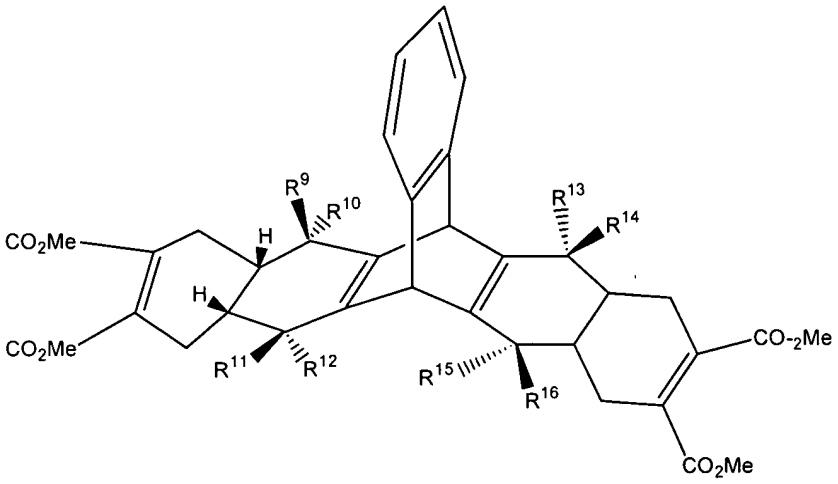

TT4: $R^9 = R^{10} = R^{11} = R^{12} = R^{13} = R^{14} = R^{15} = R^{16} = O$

TT12: $R^9 = R^{11} = R^{13} = R^{15} = H$, $R^{10} = R^{12} = R^{14} = R^{16} = OH$ "

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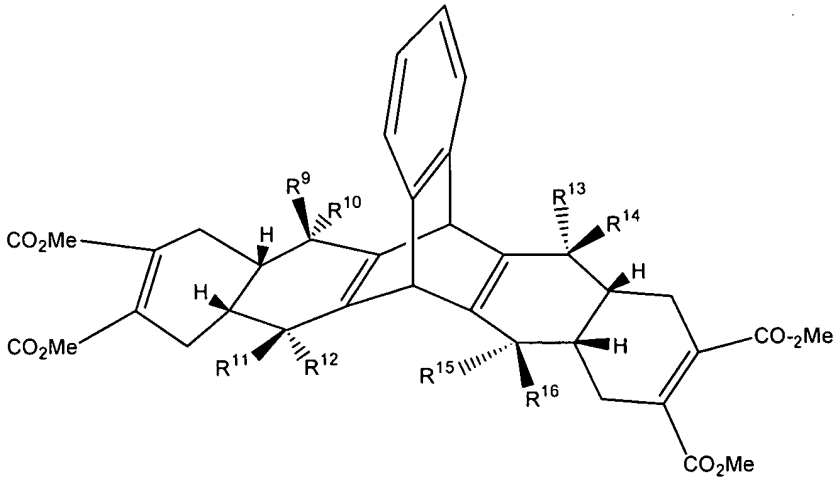
with --



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Column 15, line 52, replace "combinations thereof" with -- combinations thereof. --.

Column 34, lines 57-65, Scheme 3, insert -- + -- after the structure.

Column 37, lines 23-63, Scheme 6, replace all structures shown in Scheme 6 with

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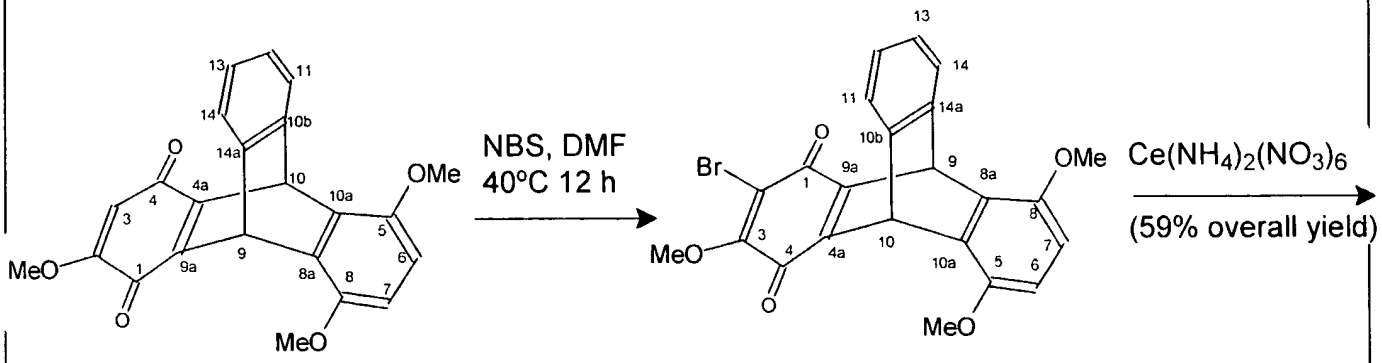
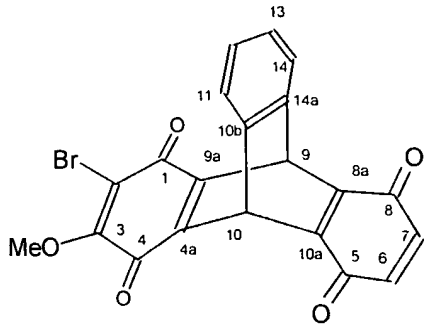


TT5 **9**



TT13

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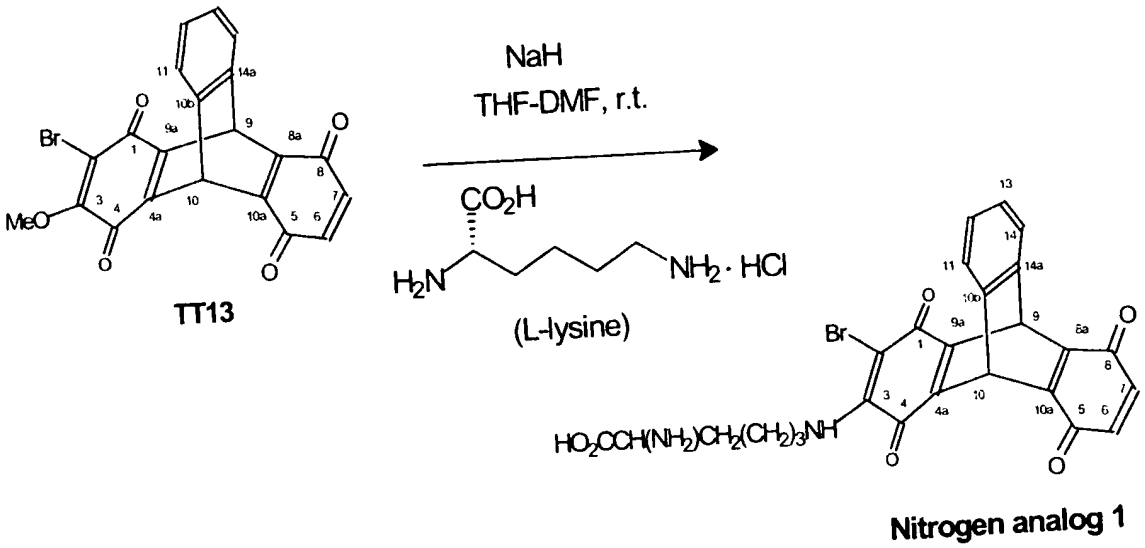

TT13

Nitrogen analog 1

--.

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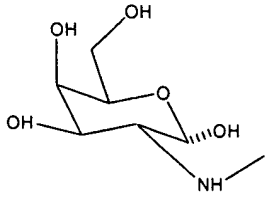

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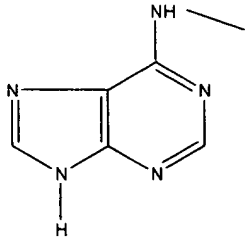

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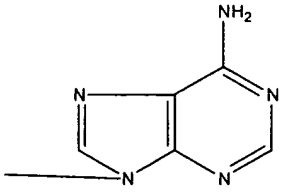

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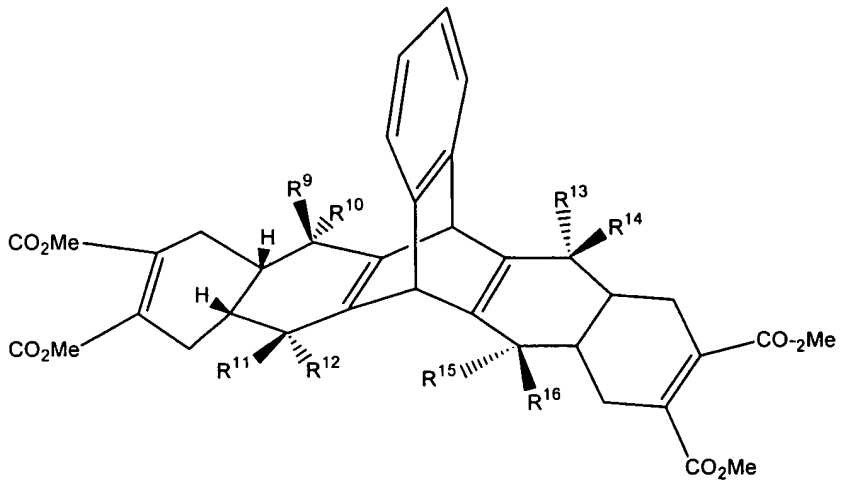

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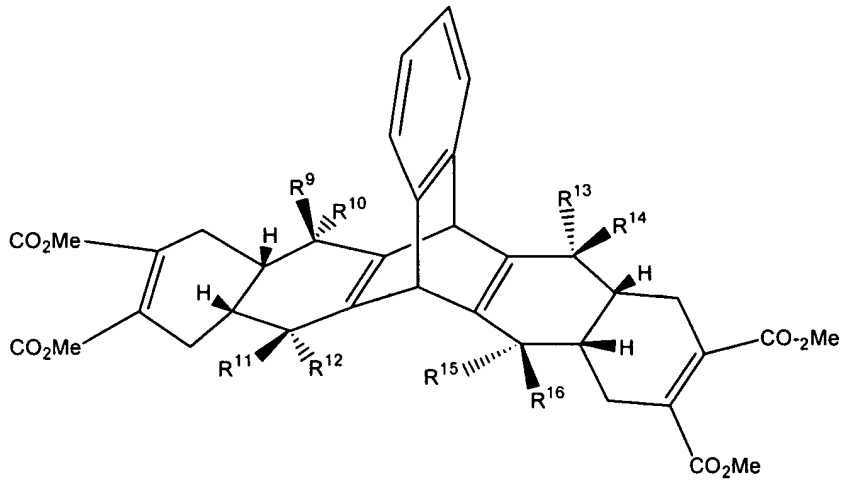

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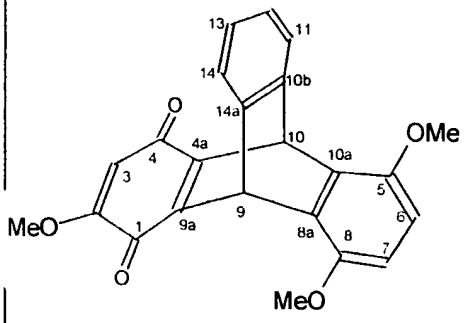
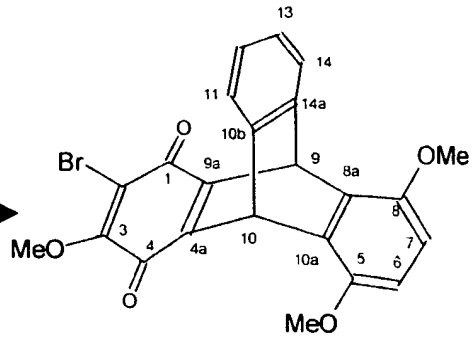


TT5

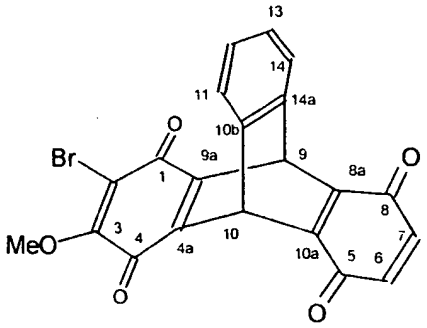
NBS, DMF
40°C 12 h



9

$Ce(NH_4)_2(NO_3)_6$

(59% overall yield)



TT13

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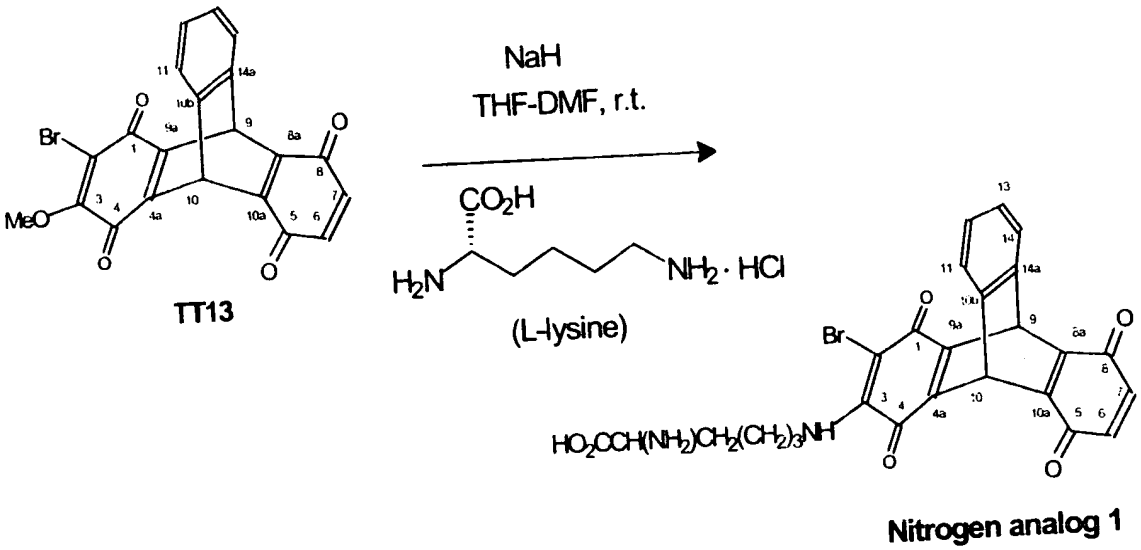

TT13

Nitrogen analog 1

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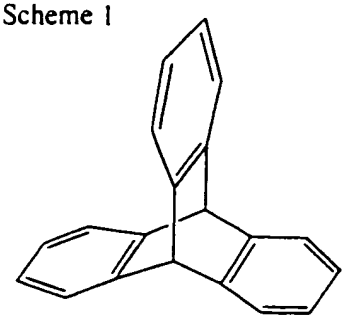
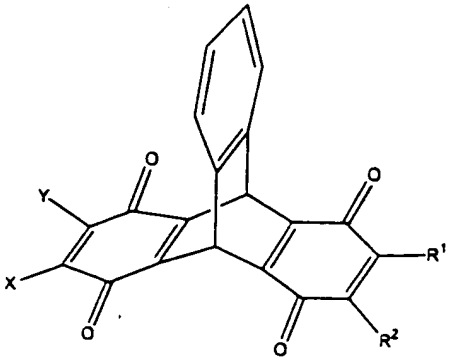
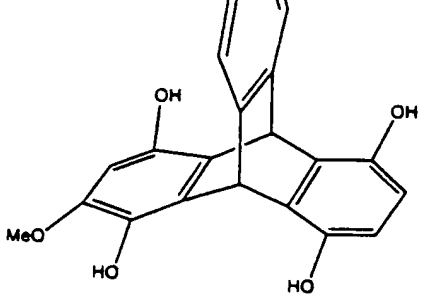
Scheme 1



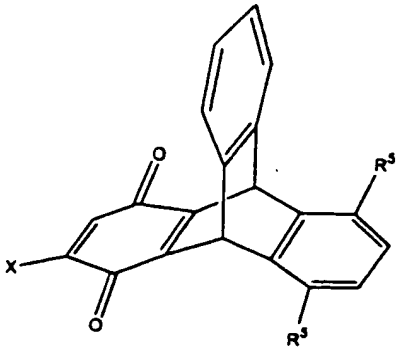
TT0: triptycene



TT1: X = Y = H
TT2: X = OMe, Y = H
TT13: X = OMe, Y = Br
TT14: X = NHMe, Y = Br
TT15: X = MHNe, Y = OH
TT16: X = OMe, Y = Br, R^2 = NMe_2
TT17: X = $NHCH_2CH_2CO_2H$, Y = Br
TT18: X = $NHCH_2CH_2CO_2Et$, Y = OH
TT19: X = $NH(CH_2)_3CH_2(NH_2)CHCO_2H$, Y= Br
TT20: X = $NH(CH_2)_3CH_2(NH_2)CHCO_2H$, Y = OH
TT21: X = $NHCH_2CH_2CO_2H$, Y = OH
TT24A: X = OMe, Y = Br, R^2 = NHMe
TT24B: X = OMe, Y = Br, R^1 = NHMe
N analog 1: X = $NH(CH_2)_3CH_2(NH_2)CHCO_2H$, Y = Br

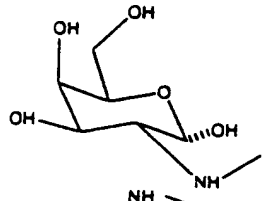


TT3



TT5: X = R^5 = OMe
TT7: X = R^5 = H
TT9: X = OMe, R^5 = H

N analog 2: Y = Br, X =



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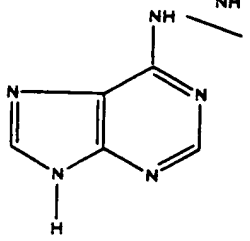

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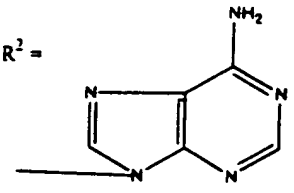

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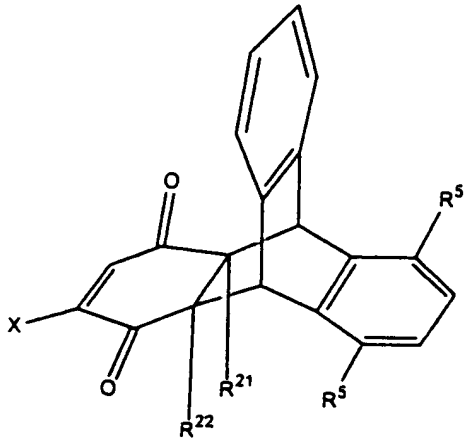
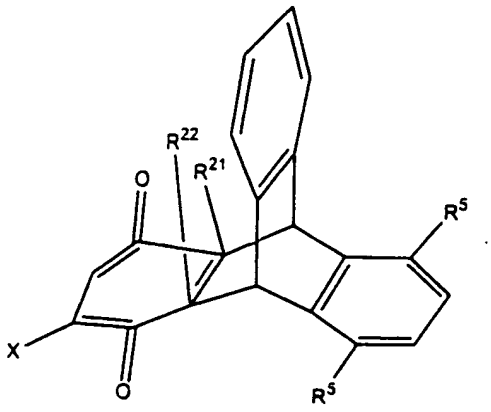
Scheme I (continued)



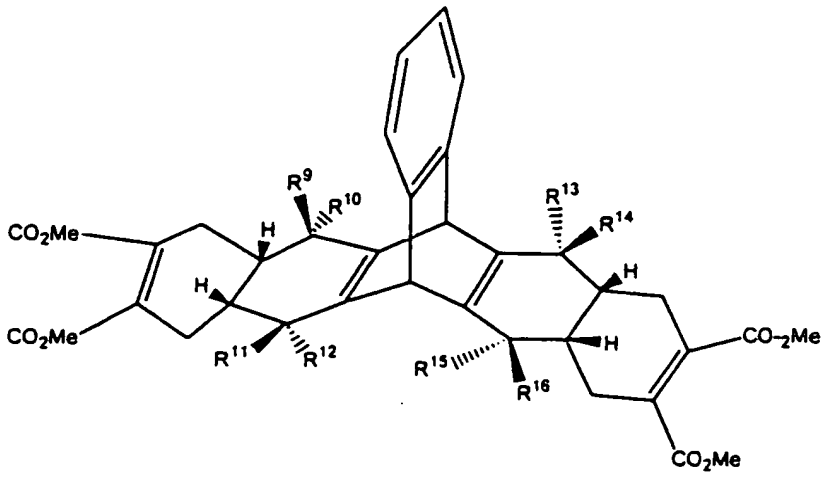
TT6: $X = R^5 = R^{21} = R^{22} = H$

TT8: $X = OMe$, $R^5 = R^{21} = R^{22} = H$

TT10: $X = CO_2Me$, $R^5 = OMe$, $R^{21} = R^{22} = H$



TT11: $X = H$, $R^5 = OMe$, $R^{22} = H$, $R^{21} = CO_2Me$



TT4: $R^9 = R^{10} = R^{11} = R^{12} = R^{13} = R^{14} = R^{15} = R^{16} = O$

TT12: $R^9 = R^{11} = R^{13} = R^{15} = H$, $R^{10} = R^{12} = R^{14} = R^{16} = OH$

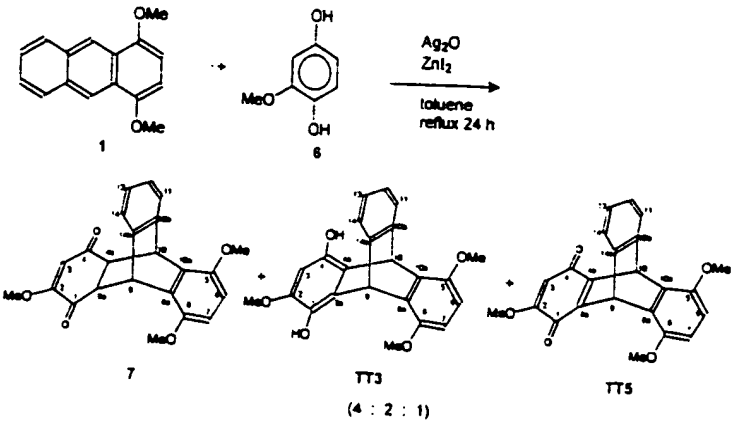
carbocyclic rings and combinations of such groups. The term also includes straight-chain, branched-chain and cyclic structures or combinations thereof. Hydrocarbyl groups are optionally substituted. Hydrocarbyl substitution includes substitution at one or more carbons in the group by moieties containing heteroatoms. Suitable substituents for hydrocarbyl groups include but are not limited to halogens, including chlorine, fluorine, bromine and iodine, OH, SH, NH_2, COH, CO_2H, OR_a, SR_a, NR_aR_b, $CONR_aR_b$, where R_a and R_b independently are alkyl, unsaturated alkyl or aryl groups.

The term "alkyl" takes its usual meaning in the art and is intended to include straight-chain, branched and cycloalkyl groups. The term includes, but is not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,1-dimethylpropyl, n-hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2-ethylbutyl, 1-ethylbutyl, 1,3-dimethylbutyl, n-heptyl, 5-methylhexyl, 4-methylhexyl, 3-methylhexyl, 2-methylhexyl, 1-methylhexyl, 3-ethylpentyl, 2-ethylpentyl, 1-ethylpentyl, 4,4-dimethylpentyl, 3,3-dimethylpentyl, 2,2-dimethylpentyl, 1,1-dimethylpentyl, n-octyl, 6-methylheptyl, 5-methylheptyl, 4-methylheptyl, 3-methylheptyl, 2-methylheptyl, 1-methylheptyl, 1-ethylhexyl, 1-propylpentyl, 3-ethylhexyl, 5,5-dimethylhexyl, 4,4-dimethylhexyl, 2,2-diethylbutyl, 3,3-diethylbutyl, and 1-methyl-1-propylbutyl. Alkyl groups are optionally substituted. Lower alkyl groups are C_1-C_6 alkyl and include among others methyl, ethyl, n-propyl, and isopropyl groups.

The term "cycloalkyl" refers to alkyl groups having a hydrocarbon ring, particularly to those having rings of 3 to 7 carbon atoms. Cycloalkyl groups include those with alkyl group substitution on the ring. Cycloalkyl groups can include straight-chain and branched-chain portions. Cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl. Cycloalkyl groups can optionally be substituted.

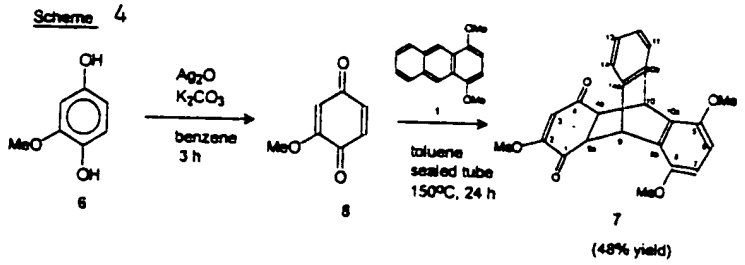
Aryl groups may be substituted with one, two or more simple substituents including, but not limited to, lower alkyl, e.g., methyl, ethyl, butyl; halo, e.g., chloro, bromo; nitro; sulfato; sulfonyloxy; carboxy; carbo-lower-alkoxy, e.g., carbomethoxy, carbethoxy; amino; mono- and di-lower-alkylamino, e.g., methylamino, ethylamino, dimethylamino, methylethylamino; amido; hydroxy; lower-alkoxy, e.g., methoxy, ethoxy; and lower-alkanoyloxy, e.g., acetoxy.

Scheme 3



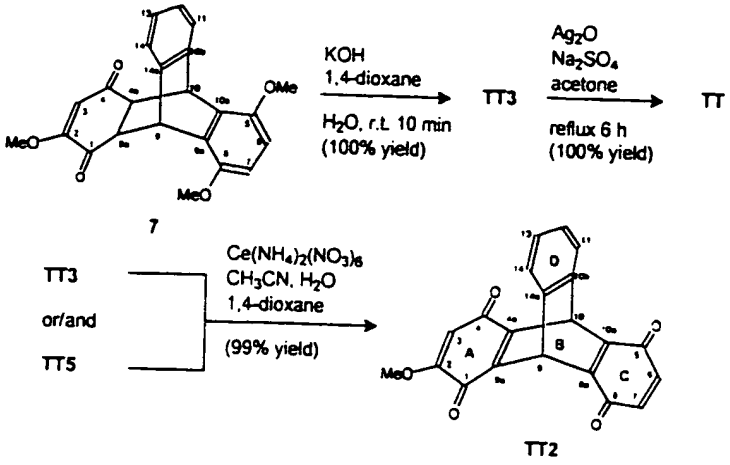
Alternatively, 7 can be obtained from the Diels-Alder reaction of quinone **8** with anthracene **1** (Scheme 4). Hence, oxidation of **6** with 1.5 equiv of silver oxide and 1.2 equiv of potassium carbonate in benzene at 25 °C for 3 h afforded quantitative yield of quinone **8** which underwent cycloaddition with **1** gave a 48% yield of 7 as a mixture of endo- and exo-isomers (a ratio of 1:1) at C4a and C9a.

Scheme 4



Diketone 7 was converted into hydroquinone **TT3** with 10 equiv of KOH in 1,4-dioxane and water at 25 °C for 1 h in quantitative yield (Scheme 5). Oxidation of **TT3** with 2 equiv of silver oxide and sodium sulfate (anhydrous) in dried acetone under reflux for 6 h gave **TT5** in quantitative yield. Oxidation of **TT5** or **TT3** or a mixture of **TT3** and **TT5** with ceric ammonium nitrate in acetonitrile-1,4-dioxane-water at 25 °C for 12 h gave excellent yields of **TT2**.

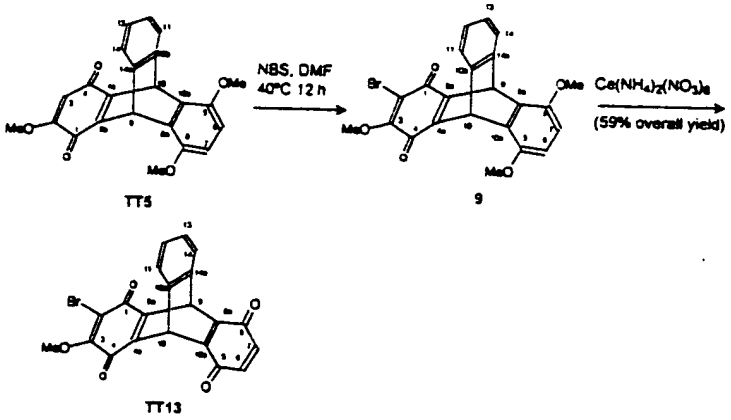
Scheme 5



Selective Bromination of 2-Methoxy Triptycene Quinone:

A new bromination reaction was found (Scheme 6). Hence, when **TT5** was treated with *N*-bromosuccinimide (NBS) in DMF at 40 °C for 12 h, a quantitative yield of the C-2 brominated product **9** was obtained. Without purification, compound **9** was directly subjected to the ceric ammonium nitrate oxidation and a 59% yield of **TT13** was achieved.

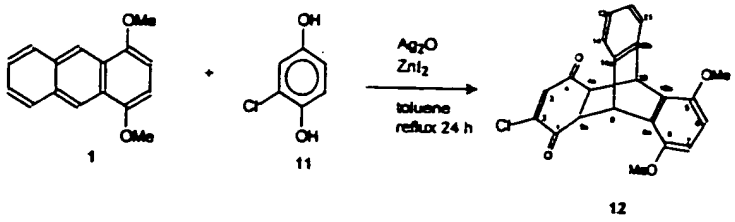
Scheme 6



Syntheses of 2-Chloro-4a,9,9a,10-tetrahydro-9,10-[1',2']benzenoanthracene-1,4-dione (10), TT8, TT9 and TT7:

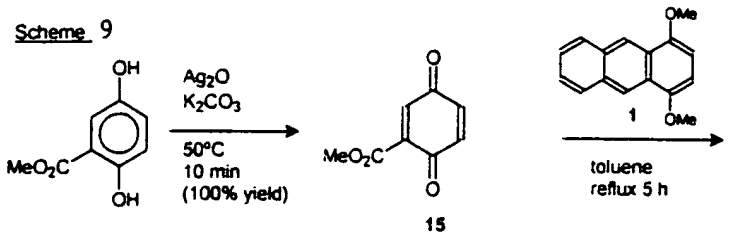
The *in-situ* oxidation and cyclization reaction is applicable to other hydroquinone substrates. For instance, 2-chlorohydroquinone (**11**), under similar reaction conditions, reacted with 1,4-dimethoxyanthracene (**1**) in the presence of silver oxide and zinc iodide under refluxing toluene to give a 73% yield of the chloro derivative **12** (Scheme 7).

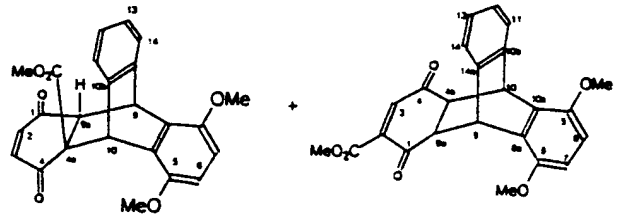
Scheme 7



of potassium carbonate in benzene at 50 °C for 10 min under dark gave a quantitative yield of the corresponding quinone **16** (Scheme 9). Diels-Alder reaction of **15** and anthracene **1** at 70 °C for 14 h and then under reflux for 5 h gave 58% yield of **TT11** (as a mixture of endo- and exo-isomers) and 37% yield of **TT10**.

Scheme 9





TT11 TT10

Syntheses of **TT4** and **TT12**:

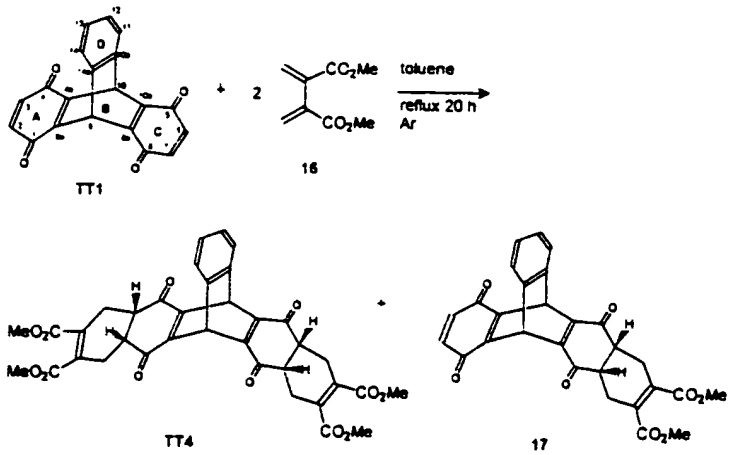
The triptycene bis-quinones such as **TT1** could be treated with dienes to produce various substituted triptycene analogs such as **TT4** and **TT12** (Scheme 10). Hence, treatment of **TT1** with 2.2 equiv of dimethyl butadiene-2,3-dicarboxylate (**16**) (Hamon, et al., J. Chem. Soc. Chem. Commun. 1981, 873-4) in toluene under reflux for 20 h gave a 54% yield of **TT4** and 14% yield of monoadduct **17**. The stereochemistry of **TT4** was firmly established by a single-crystal X-ray analysis. Reduction of **TT4** with 10 equiv each of sodium borohydride and cerium trichloride heptahydrate in MeOH at room temperature for 12 h afforded an 89% yield of TT12. The ^{1}H and ^{13}C NMR spectrum of TT12 indicated a single stereoisomer. It is anticipated that the hydride (sodium borohydride) should attack the carbonyl group from the exo face (b-face) and the stereochemistry is therefore assumed.

Syntheses of **TT14**, **TT15**, and **TT16**:

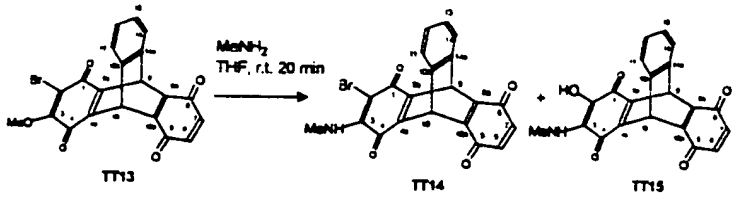
Bromomethoxyquinone **TT13** can be converted into methylaminoquinone **TT14** in 25% yield along with a 29% yield of **TT15** by the treatment with methylamine in THF at room temperature for 20 min (Scheme11). This reaction is unusual in that the nucleophile, methylamine, displaces the methoxy group of **TT13** instead of the bromine. Again,

unexpectedly, when **TT13** was treated with dimethylamine in THF at 0°C, **TT16** was isolated as the only identificable product (Scheme 12). The regiochemistry of the dimethylamino group of **TT16** is tentatively assigned.

Scheme 10



Scheme 11



Similar to the addition reaction of methylamine with **TT13**, other primary amines, such as ethyl b-alanine and L-lysine also add to **TT13** to provide the corresponding amino acid adducts **TT17 ~ TT20** (Scheme 13). Hence, treatment of TT13 with ethyl b-alanine (derived from ethyl b-alanine hydrochloride with 1 equiv of sodium hydride in THF) in THF and DMF at 25°C to give a mixture of **TT17** and **TT18** (based on the proton NMR spectrum of the crude product). Column chromatographic separation on silica gel gave **TT18** in 69% yield. The ethyl ester function of **TT18** can be removed by treatment with sodium iodide in DMF with heat to give amino acid **TT21** which is water soluble.

Dimethyl 1,3-butadiene-2,3-dicarboxylate (**16**):

To a solution of 6.53 g (0.02 mol) of bromoesters **22** in 20 mL of acetone was added 9.49 g (0.06 mol) of sodium thiosulphate and 9.96 g (0.06 mol) of potassium iodide. After refluxing for 2 hr., The mixture was cooled, poured onto 50 g of ice, and extracted with methylene chloride three times (150 mL once, 50 mL twice). The combined methylene chloride extracts were washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, concentrated, and column chromatographed on silica gel using a gradient mixture of hexane- ethyl acetate as eluant to give 2.8206 g of butadiene **16** in a yield of 83%. ^{1}H NMR ($CDCl_3$) d 6.71(dd, J = 1.4, 0.6 Hz, 2 H, =CH), 5.83 (dd, J = 1.4, 0.6 Hz, 2 H, =CH), 3.76 (s, 6 H, OMe); ^{13}C NMR ($CDCl_3$) d 166.20 (s, C=O), 138.42 (s, =C), 127.79 (t, $=CH_2$), 52.09 (q, OMe).

(4a*S**,7a*R**,11a*S**,14a*R**)-Tetramethyl 1,4,4a,5,6,7,7a,8,11,11a,12,13,14,14a-tetradecahydro-5,7,12,14-tetraoxo-6,13-[1',2']benzenopentacene-2,3,9,10-tetracarboxylate (TT4) and Compound 17:

A solution of 0.14 g (0.45 mmol) of **TT1** and 0.17 g (1 mmol) of compound **16** in 5 mL of toluene was maintained under argon and heated under reflux for 22 h. The solution was directly subjected onto a silica gel column and eluted with a gradient mixture of hexane, methylene chloride, and ethyl acetate to give 0.160 g (54% yield) of **TT4** and 30 mg (14% yield) of compound **17**. Recrystallization of **TT4** from methylene chloride gave light yellow crystals. Single crystal X-ray diffraction analysis was carried on a crystal and the structure was solved. The following Figure shows the ORTEP drawing of the compound. ^{1}H NMR ($CDCl_3$) d 7.45 (m, 2 H), 7.09 (m, 2 H), 6.07 (s, 2 H, C6,13 Hs), 3.75 (s, 12 H, OMe), 3.2 (bs, 4 H, C4a,7a,11a,14a Hs), 2.62 ~ 2.5 (m, 8 H); ^{13}C NMR ($CDCl_3$) d 192.36 (s, C=O), 167.12 (s, C=O of ester), 154.04 (d), 141.49 (s), 132.51 (d), 126.02 (s), 125.57 (s), 52.33 (q, OMe), 45.5 (d), 43.27 (d), 25.48 (t).

Compound **17**: ^{1}H NMR ($CDCl_3$) d 7.42 (dd, J = 5, 3 Hz, 2 H), 7.01 (dd, J = 5, 3 Hz, 2 H), 6.38 (s, 2 H), 6.10 (s, 2 H), 3.71 (s, 6 H, OMe), 3.17 (bs, 2 H, CHC=O), 2.60 (dd, J = 17, 4 Hz, 2 H), 2.43 (dd, J = 17, 4 Hz, 2 H). (19).

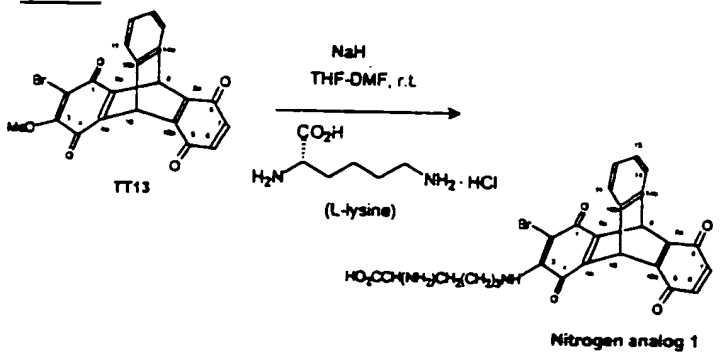
Compound **TT24**: ^{1}H NMR ($CDCl_3$) δ 7.44 – 7.40 (m, 2 H), 7.03 (m, 2 H), 6.27 (s, 1 H), 6.15 and 6.14 (2 s, 1 H), 5.69 (q, J = 5.6 Hz, NH), 5.26 (s, 1 H), 3.80 & 3.79 (2 s, 3 H, OMe), 2.79 (d, J = 5.6 Hz, 3 H, NMe); ^{13}C NMR ($CDCl_3$) δ 181.7, 181.6, 179.5, 156.2, 147.8, 147.6, 143.9, 143.8, 143.6, 142.3, 141.8, 141.3, 139.6, 139.1, 131.2, 126.9, 125.52, 125.49, 125.46, 125.4, 124.8, 124.75, 124.3, 124.2, 102.3, 95.8, 95.7, 61.1, 60.4, 42.2, 41.9, 41.3, 41.0, 29.3 (2 C).

SYNTHESIS OF OTHER N ANALOGS AND S ANALOGS

As illustrated in Scheme 17, nitrogen analog **1** has been prepared. Treatment of **TT13** with 1 equivalent each of L-lysine hydrochloric acid and sodium hydride in a 1:1 mixture of THF and DMF under argon at room temperature gave amino acid analog **1** which is a water soluble drug.

Scheme 19 outlines the synthetic route to prepare nitrogen analogs 2-4. Treatment (Kenani, A.; Bailly, C.; Helbecque, N.; Houssin, R.; Bernier, J. -L.; Henichart, J. -P. *Eur. J. Med. Chem.* **1989**, *24*, 371-377.) of D-galactosamine hydrochloride (commercially available) with sodium hydroxide and di-*t*-butylcarbonate in 1,4-dioxane and water, followed by protection of the hydroxyl function with excess of acetyl anhydride in pyridine, and removal of the Boc protecting group with hydrochloric acid in 1,4-dioxane produces amine **6**. Addition of **6** with **TT13** in THF at –40 °C followed by removal of the acetoxy protecting group affords nitrogen analog **2**.

Scheme 17



Similarly, glucosamine hydrochloride can be used to prepare glucosamine analog (of **2**; instead of galactosamine analog).